

# **EXHIBIT 12**

Sex and racial disparities in cardiovascular risk continue to exist, and the risk factors fueling these disparities will require redress. The enormous progress in reducing cardiovascular disease mortality realized since the 1960s represent public health and health care improvement successes, yet more progress in reducing the remaining colossal burden of cardiovascular disease in the United States awaits.

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## Prescription Drug Abuse: A National Survey of Primary Care Physicians

Chronic pain is one of the most common reasons for seeking medical attention in the United States, and such pain is frequently treated with prescription opioids.



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The clinical use of these products nearly doubled between 2000 and 2010,<sup>1</sup> with simultaneous increases in the incidence of opioid abuse, addiction, injury, and

death.<sup>2</sup> Because primary care physicians play a critical role in maximizing the safe use of these products, we examined their beliefs and self-reported practices regarding prescription opioid use.

Table 1. Physician Characteristics

Characteristic	Value (N = 420)
Age, mean (SE), y	50 (0.4)
Male sex, %	55
Specialty, %	
Family practice	52
Internal medicine	46
General practice	2
Ethnicity, %	
White	70
Asian	19
African American or other	11
Practice type, % <sup>a</sup>	
Solo or small group practice	45
Academic medical center-based practice	13
Managed care organization	12
Public or government-based practice	11
Other	23
Works in academic or teaching hospital, %	24
Ownership in practice	
Full	21
Partial	14
None	65
No. of patients seen per month, mean (SE)	285 (8.4)
No. of patients prescribed an opioid per month, mean (SE)	35 (2.9)
Pharmaceutical companies visit primary site of clinical practice, %	56

Abbreviation: SE, standard error.

<sup>a</sup> Column total may exceed 100% because more than 1 response may apply.

**Methods |** We used the Dillman<sup>3</sup> approach to conduct a nationally representative postal mail survey. We sampled 1000 practicing US internists, family physicians, and general practitioners using the American Medical Association Masterfile. Participants were sent a questionnaire, \$2 cash incentive, and self-addressed stamped envelope in February 2014, and non-respondents were contacted a maximum of 3 times in approximately 6-week intervals. Response patterns between early and late responders were similar, suggesting the absence of non-response bias. However, because of modest sociodemographic differences between respondents and nonrespondents, we incorporated poststratification weights in our analyses. The questionnaire and study protocol were exempted from review by the institutional review board of the Johns Hopkins Bloomberg School of Public Health. The study did not require informed consent because it did not qualify as human subjects research.

**Results |** Our adjusted response rate was 58%, and physician characteristics are reported in Table 1. Most physicians (90%) reported prescription drug abuse to be a “big” or “moderate” problem in their communities, and more than four-fifths (85%) reported that opioids are overused in clinical practice (Table 2). A majority of physicians (65%-84%) reported being “very” or

Table 2. Attitudes and Beliefs Regarding the Use of Opioids in Clinical Practice

Attitude or Belief	Respondents, % (N = 420)			
	No Problem at All	A Small Problem	A Moderate Problem	A Big Problem
<b>Belief Regarding Prescription Drug Abuse</b>				
Magnitude of prescription drug abuse in the community	0	10	37	53
	Strongly Disagree	Somewhat Disagree	Somewhat Agree	Strongly Agree
<b>Belief Regarding Opioid Use in Clinical Practice</b>				
In general, opioids are overused to treat pain today	2	13	39	46
Patients commonly embellish or fabricate their pain symptoms to obtain opioids	3	15	46	36
	Not at All	Slightly	Moderately	Very
<b>Attitude Toward Opioid Prescribing</b>				
Confidence in clinical skills related to opioid prescribing	2	10	56	32
Comfort in prescribing opioids for chronic noncancer pain	13	38	36	13
<b>Concern About Potential Patient Outcomes</b>				
Addiction	1	15	29	55
Deaths related to opioids	6	24	22	48
Motor vehicle accidents related to opioids	1	22	33	44
Nonadherence	11	24	32	33
Tolerance	3	22	44	31
Impaired cognition	1	25	44	30
Sedation	2	27	44	27
<b>Concern About Potential Prescriber Outcomes</b>				
Malpractice claim	17	37	20	26
Prosecution	25	30	20	25
Censure by state medical board	26	30	19	25
	Never	Rarely	Sometimes	Often
<b>Belief Regarding Frequency of Potential Adverse Events When Opioids Are Used as Directed</b>				
Tolerance	0	5	33	62
Physical dependence	1	6	37	56
Ceiling effects	1	9	54	36
Addiction	1	22	50	27
Hypersensitivity to pain (hyperalgesia)	3	27	43	27

“moderately” concerned about each potential adverse patient outcome that was assessed, including opioid-related addiction (55% reporting “very concerned”), deaths (48%), and motor vehicle accidents (44%). Furthermore, most physicians reported high frequencies of adverse events—such as tolerance (62% reported occurring “often”), physical dependence (56%), and ceiling effects (36%)—even when prescription opioids are used as directed to treat chronic pain. Physicians expressed somewhat lower degrees of concern for potential adverse prescriber outcomes associated with opioid prescribing, such as malpractice claims and censure by state medical boards. Approximately one-half of physicians (45%) reported being less likely to prescribe opioids compared to 1 year ago. Despite this, nearly all physicians (88%) expressed confidence in their clinical skills related to opioid prescribing, and nearly one-half (49%) were “very” or “moderately” comfortable using these drugs for chronic noncancer pain.

**Discussion |** Primary care physicians appear to recognize many elements of the prescription drug abuse epidemic, such as the high prevalence of adverse outcomes associated with opioid

use.<sup>4,5</sup> Although our study did not allow for longitudinal assessment of these physicians’ attitudes or knowledge over time, substantial publicity and raising of awareness on the part of many stakeholders may have contributed to these findings. Physicians’ high levels of confidence in their own prescribing are also of note and may reflect a combination of their experiences, as well as cognitive biases that have been demonstrated in other settings.<sup>6,7</sup>

Our study has limitations. First, our results are based on self-report and prone to socially desirable response bias. We minimized this potential by ensuring participant confidentiality and avoiding leading questions. Second, nonresponse bias may have influenced our findings. To reduce this impact, we maximized survey participation rates using the Dillman method and implemented poststratification weights in our analyses.

Given the increasing use of opioids in clinical practice and its attendant morbidity and mortality, understanding primary care physicians’ prescribing patterns, as well as their perception of adverse events associated with the use of these products, is crucial. Our investigation suggests that most primary

care physicians are aware of many risks of opioids, and many have decreased their prescribing of these products during the past 12 months.

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**Conflict of Interest Disclosures:** Ms Hwang is a current ORISE Fellow at the Food and Drug Administration. Dr Kruszewski has served as a general and case-specific expert for multiple plaintiff litigations involving OxyContin, Neurontin, and Zyprexa and has had false claims settled as coplaintiff with the United States against Southwood Psychiatric Hospital, Pfizer (Geodon), and AstraZeneca (Serquel). Dr Kolodny is employed by the Phoenix House and is President of Physicians for Responsible Opioid Prescribing. Dr Alexander is Chair of the Food and Drug Administration's Peripheral and Central Nervous System Drugs Advisory Committee, serves as a paid consultant to IMS Health, and serves on an IMS Health scientific advisory board. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. No other disclosures are reported.

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## Association of Cardiovascular Trial Registration With Positive Study Findings: Epidemiological Study of Randomized Trials (ESORT)

Trial registration has been proposed to reduce selective publication and outcome reporting, thereby increasing accountability in the conduct of research.<sup>1</sup> Since 2005, policy makers, journal editors, and research funders have increasingly endorsed and mandated trial registration.<sup>2</sup> However, evidence to support the proposed benefits of trial registration is lacking. Analysis of a select group of randomized trials (RTs) in oncology found that registered and unregistered trials were equally likely to reach conclusions favoring new oncology drugs.<sup>3</sup> We conducted a cross-sectional analysis of published cardiovascular RTs to compare RTs reported as registered with those not reported as registered.

**Methods |** An RT was eligible for analysis if it was published on PubMed in December 2012 and focused on a cardiovascular disease, as defined by the *International Classification of Diseases*. Our research group<sup>4</sup> has previously reported a detailed description of the process. Briefly, 2 reviewers independently screened all abstracts and full texts. No language restrictions were applied. Study characteristics and methodological characteristics (Table 1) were extracted in duplicate. The International Committee of Medical Journal Editors definition of trial registration was used.<sup>1</sup> The primary outcome was the reported study findings for each trial, categorized as significant positive, nonsignificant, or significant negative. Trials not reported as registered were searched for registry information using the World Health Organization Trials Registry Platform. The  $\chi^2$  test, Fisher exact test, and Wilcoxon rank-sum test were applied as appropriate for analysis.

**Results |** We identified 4190 abstracts of possible reports of RTs, among which 191 cardiovascular RTs were identified. Of these, 86 (45.0%) were reported as registered. Registry information was found for 6 (5.7%) of the 105 trials not reported as registered. Trials reported as registered (median sample size, 111; interquartile range [IQR], 49-360) were larger than those not reported as registered (median sample size, 59; IQR, 24-106) ( $P < .001$ ). Trials reported as registered were also more likely to report a power calculation, explicitly define the primary outcome, and report attrition among study participants. Specific data are reported for all characteristics in Table 2;  $P < .05$  for all comparison.